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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,509	06/13/2005	Herman Jan Tijimen Coelingh Bennink	0470-045922	1291

28289 7590 03/31/2010

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EXAMINER	
JEAN-LOUIS, SAMIRA JM	
ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
03/31/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,509	COELINGH BENNINK ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-19 and 21-34* is/are pending in the application.

4a) Of the above claim(s) *17,21-23,25,27 and 29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-19, 24, 26, 28, and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/09, 10/20/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

This Office Action is in response to the amendment submitted on 12/18/09. Claims 17-19 and 21-34 are currently pending in the application, with claims 1-16 and 20 having being cancelled and claims 17, 21-23, 25, 27, and 29-31 having being withdrawn. Accordingly, claims 18-19, 24, 26, 28, and 32-34 are being examined on the merits herein.

Receipt of the aforementioned amended claims and Information Disclosure Statements (IDS) is acknowledged and has been entered.

Applicant's argument with respect to the rejection of claims 18-20, 24, 26, 28, and 32 have been fully considered. Applicant argues that as pointed out during the interview held on 12/2/09, applicant does possess written support for "reducing the risk of developing". Moreover, Applicant contends that applicant should not be held to a standard that the specification must provide data establishing prevention. Such arguments are not however persuasive as the Examiner maintains that does not possess support for a method of reducing the risk of developing vaginal dryness. While applicant recited the limitation that the method may be applied to healthy skin or skin already dry, flaked, lined, wrinkled, aged, or photodamaged to prevent or reduce such deteriorating changes (i.e. reducing the dry, flaky, lined, wrinkled, aged and photodamaged skin; see pg. 3, lines 8-15), applicant does not possess support for a

method of reducing the risk of developing vaginal dryness. As a result, the Examiner contends that such recitation does not provide support for reducing the risk of developing vaginal dryness. What the Examiners did mention to applicant during the interview is that given the lack of data for preventing vaginal dryness and given that reducing the risk encompasses prevention as well, the Examiners contend that an enablement rejection can potentially be made. Nonetheless, the Examiner maintains that due to lack of written support of the aforementioned limitation, the rejection was indeed proper. However, given applicant's amendment of the claims, the 112, first paragraph rejection of claims 18-20, 24, 26, 28, and 32 is hereby withdrawn.

Applicant's argument that in light of the disclosure of Kragie and Willhite or in view of Sitruk-Ware, Spicer and in further view of Willhite, one of ordinary skill would have no reason to pick estetrol form the long list where estetrol is listed as a mere possibility rather than part of the invention has been fully considered. Such arguments are not found persuasive as the Examiner maintains that Kragie teaches compositions and methods that can replace the role of estrogens in the functions of humans. Kragie further teaches the use of Estrogen Function Replacement Agents (EFR) and cites the use various EFR agents including estetrol (i.e. applicant's elected species in claim 28). Additionally, Kragie teaches that the EFR agent would be dosed to provide sufficient biological activity for the desired estrogen function at the tissue target and at a dosage that would minimally meet the EC50 value of the desired estrogenic function (see paragraph 0044). Moreover, Kragie teaches that weak (i.e. less potent) estrogenic

compounds can be used and can possess both partial agonist and partial antagonist characteristics (paragraph 0044). Additionally, Kragie teaches the use of the EFR agents for various clinical conditions including treatment of vaginal atrophy and relief of urogenital atrophy (see paragraph 0073). As a result, the Examiner contends that while estetrol is listed in a list of EFR agents, Kragie specifically teaches that the list contains EFR agents include agents that are weak estrogenic compounds, partial agonists and partial antagonists. As a result, the Examiner contends that Kragie did indeed envision the use of weak agents such as estetrol in his invention since he acknowledges the use of weak agents to be used in his invention. Thus, it would have been well within the purview of the skilled artisan to utilize and to try estetrol since Kragie specifically teaches the use of estetrol as an EFR agent in the treatment of vaginal atrophy and urogenital atrophy. Moreover, given the teaching of Kragie where weak EFR agents can be used at the appropriate dosage in order to provide sufficient biological activity for the desired estrogen function at the target site, the Examiner maintains that such teachings would provide the motivation for one skilled in the art to utilize and try such agents and one of ordinary skill in the art would have had a reasonable expectation of success since Kragie teaches that dosages can be adjusted in order to obtain the proper biological effect. Thus, regardless if no one appreciated the long half-life of estetrol, the Examiner maintains that it would have indeed been obvious to try estetrol given that Kragie teaches its use for the treatment of vaginal atrophy and urogenital atrophy and given that Kragie listed a finite number of predictable EFR agents to be used for the aforementioned treatment. The Examiner further maintains that Kragie did

envisage the use of weak EFR agents such as estetrol since Kragie clearly teaches using weak EFR agents and further discloses that appropriate dosage would be dosed in order to provide sufficient biological activity for the desired estrogen function. Thus, the Examiner maintains that estetrol was indeed taught by Kragie to be used for vaginal dryness and that Kragie did indeed envision weak EFR agents and thus estetrol.

As for applicant's argument that Examiners Hui and Chui withdrew their rejections over the co-pending applications after the interview and declaration of Dr. Westhoff and thus applicant is providing the same references to overcome the 103 (a) rejection, the Examiner however maintains that each application is examined based on its own merit. Moreover, the Examiner would like to point out that while Applicant argues that the art and one of ordinary skill in the art was not aware of the half-life of estetrol and thus would not have selected estetrol, the Examiner contends that estetrol was explicitly taught out of a list of EFR agents to be useful for the treatment of vaginal or urogenital atrophy. Importantly, Kragie also teaches that weak EFR agents which include estetrol, partial agonists and antagonists could be used for the aforementioned treatment and appropriate dosages could be modified in order to obtain the proper biological function. As a result, the Examiner maintains that while Kragie did not recognize the binding affinity of E4, its discovery by appellants is tantamount only to finding a property in the old composition." 363 F.2d at 934, 150 USPQ at 628. Unlike Examiners Hui and Chui, the current Examiner did not made a substitution rationale for estetrol in Kragie but rather stated that one of ordinary skill in the art would have found it obvious to try estetrol in view of the explicit disclosure of Kragie.

Moreover, the Examiner respectfully points out that while applicant states that estetrol can be classified as a SERM and SERMs have a stimulatory effect on breast tumors and thus would not be selected as an agent for vaginal dryness, the Examiner disagrees with such argument as the characterization of estetrol being a SERM was not considered till 2008, long after the filing date of the invention. Consequently, one of ordinary skill at the time of the invention would not have concluded that estetrol is a SERM and would have found it obvious to utilize and try estetrol as indicated by Kragie. Though applicant continues to argue that applicant found the unexpected results of estetrol being potent and possessing a long elimination half-life, the Examiner maintains that such results are neither unobvious nor unexpected since Kragie suggested the use of estetrol for urogenital atrophy, also known as vaginal dryness.

As for Willhite, it was provided to demonstrate that urogenital atrophy is also known as vaginal dryness. As a result, Kragie in view of Willhite and Sitruk-Ware in view of Spicer and in view of Willhite does indeed render obvious applicant's invention.

Applicant's argument that Younglai does not render obvious claim 28 as amended has been fully considered. Applicant argues that claim 28 as amended requires the precursors to be derivatives of the formula delineated in claim 28. Such arguments are not however found persuasive as the Examiner contends that applicant is arguing the newly amended claim. Moreover, the Examiner contends that given that applicant has cancelled claim 20, such argument is now moot. While applicant incorporated claim 20 into claim 28, the Examiner points out that the requirement for

claim 28 is to provide at least one estrogenic component selected from the group delineated in claim 28 along with a cosmetically acceptable vehicle. As a result, the Examiner is under no obligation to meet the limitation of the precursor derivatives. However, in light of applicant's cancellation of claim 20, the rejection of claim 20 in view of Younglai is hereby withdrawn.

For the foregoing reasons, the rejections of record were indeed proper. However, in view of applicant's amendment, the following modified 112, first paragraph and 103 (a) Final rejections are being made.

IDS

The information disclosure statement filed on October 20, 2008 (specifically item 23 (Erdbruegger et al.) fails to comply with 37 CFR 1.98(a)(3) because it was not provided and no concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, was provided for the aforementioned NPL. Consequently, the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-19, 24, 26, 28, and 32-34 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. While applicant recited the limitation of a method of treating or preventing vaginal dryness, nowhere in the specification did applicant recite a method of reducing the risk of developing vaginal dryness. Rather, in the instant specification, applicant recites a method that is applied to human skin which is already dry, flaky, lined, wrinkled, aged, photodamaged, or to healthy skin to prevent or reduce such deterioration changes (i.e. reducing the dry, flaky, lined, wrinkled, aged and photodamaged skin; see pg. 3, lines 8-15). The Examiner contends that such recitation does not provide support for reducing the risk of developing vaginal dryness. Consequently, due to this lack of written description, the method of reducing the risk of developing vaginal dryness being claimed by applicant cannot be fully ascertained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-19, 24, 26, 28 and 32-34 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Kragie (U.S. 2004/0192598 A1, previously cited) in view of Willhite et al. (Pharmacotherapy, 2001, Vol. 21, Issue 4, pgs. 464-480, previously cited).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Kragie teaches the use of compositions that can replace the role of estrogens in the functions of humans (see abstract). According to Kragie, the compositions comprise estrogen function replacement agent (s) (EFR) that can selectively, partially, or totally replace the function of estrogens, such as estradiol, in the functions of humans and animals (see pg. 2, paragraph 0013 and pg. 4, paragraph 0033). Examples of such agents include *inter alia* derivatives of estradiol such as estetrol (i.e. a compound of the

aforementioned formula which reads on claim 28; see pg. 4, paragraph 0038 and pg. 11, claim 7). The dosage of the EFR agent is provided for sufficient biological activity for the desired estrogen function at the tissue target and needs to minimally meet the EC50 value (half maximal efficacy concentration; instant claim 24) for the desired estrogen function (see pg. 5, paragraph 0044) and can be administered with a suitable carrier (see pg. 6, paragraph 0051). Kragie further teaches that the compositions may be formulated for topical or transdermal applications in the form of lotions, gels, or creams and when applied as a transdermal patch for a period of 1 to 4 days wherein the patch contacts the active ingredient to a smaller surface area allowing a slow and constant delivery of the active ingredient (i.e. application more than once a day; instant claims 26 and 32; see pg. 6, paragraph 0051). Of interest, Kragie described the EFR agents containing compositions as useful for menopause and further teach that EFR agents are currently used in peri-menopausal and post-menopausal women for treatment of vaginal atrophy and urogenital atrophy (see pg. 8, paragraph 0073).

Kragie does not particularly teach a method of treating vaginal dryness using at least 5 μg/g of estetrol.

However, to one of ordinary skill in the art, it would have been obvious to optimize the appropriate dosage that would produce the desired estrogenic function since Kragie teaches that the dosages of EFR agents can be formulated to provide sufficient biological activity for the desired estrogen function at the tissue target.

Moreover, it is generally noted that differences in concentration or range do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or dosage is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Given that applicant did not point out the criticality of specific ranges or dosages of the invention, it is concluded that the normal desire of scientists or artisans to improve upon what is already generally known would provide the motivation to determine where in a disclosed set of ranges is the optimum combination of dosages.

Willhite et al. have been provided to demonstrate that urogenital atrophy is also known as vaginal dryness (see Introduction Section). Consequently, Kragie necessarily meets the limitation of claim 28 and teaches a method of treating vaginal dryness.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious utilize and obvious to try the method of Kragie with a desired amount of estetrol in the treatment of vaginal dryness since Kragie teaches the use of estradiol derivatives such as estetrol in amounts that would produce the desired estrogenic function for the treatment of urogenital atrophy. Given that Kragie teaches the use of ERF agents to treat urogenital atrophy (i.e. vaginal dryness as disclosed by Willhite et al.) using ERF agents such as estetrol, one of ordinary skill would have been motivated to utilize and try estetrol to treat vaginal dryness with the reasonable expectation of

providing a method that is efficacious in treating vaginal dryness and efficacious in producing desirable estrogenic function.

Claims 18-19, 24, 26, 28, and 32-34 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Sitruk-Ware et al. (Shweiz. Rundsch, Med. Praxis, 1997, Vol. 86, No. 33, pgs. 1-13, English Translation) in view of Spicer (U.S. 5,211,952, previously cited) and in further view of Willhite et al. (Pharmacotherapy, 2001, Vol. 21, Issue 4, pgs. 464-480, previously cited).

Sitruk-Ware et al. teach that urogenital symptoms is due to low estrogen after menopause (see pg. 2, paragraph 1). This low estrogen is further taught to lead to urogenital atrophy, vaginal irritation and vaginal dryness wherein Sitruk-Ware et al. suggest the use of estrogen to be applied to the vaginal surface to treat such symptoms (see pg. 2, paragraphs 2-3, pg. 3, paragraph 2, and pg. 4, paragraph 2). Sitruk-Ware et al. further teach that estrogenic treatment at doses necessary for making the symptoms disappear is an efficient way to correct the aforementioned symptoms (see pg. 2, paragraphs 2-4, pg. 4, paragraph 2, and pg. 10, paragraph 2). Different modes of application have been developed including vaginal creams (instant claim 32, pg. 2, last paragraph). Sitruk-Ware et al. further teach that treatments with low adverse effects and low doses are preferred (pg. 10, paragraph 4). Sitruk-Ware et al. further teach estrogen compounds at low doses such as 7.5 µg/day for prolonged release regimen in the treatment of urogenital atrophy (pg. 8, paragraph 1).

The Willhite and Sitruk-Ware et al. references are as discussed above and incorporated by reference herein. However, Sitruk-Ware and Willhite do not teach the use of an estrogenic component such as estetrol.

Spicer et al. teach preparations for use for extended period of time comprising gonadotrpopins (GnRH) and estrogenic compounds (see col. 1, lines 9-11). Spicer et al. further teach the addition of estrogenic steroids for counteracting the possibility of side effects such as urogenital atrophy which may develop during prolonged therapy (col. 3, lines 25-46). Estrogenic steroids such as estetrol may be employed in the composition for a short term administration on the order of about 5 to 20 days and formulated for vaginal delivery (instant claims 26 and 28; col. 5, lines 49-53, and 60, and col. 6, line 68). These compositions can further include a carrier vehicle known for controlled release (see col. 7, lines 1-5).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the composition of Spicer et al. in view of their efficacy in combating urogenital atrophy since Willhite et al. teach that vaginal dryness is also known as urogenital atrophy. Moreover, one of ordinary skill in the art would have found it obvious to formulate the composition of Spicer et al. as a vaginal cream since Sitruk-Ware et al. teach that creams are conventional formulations in the treatment of vaginal atrophy. Thus, given that Sitruk-Ware et al. teach a method of treating vaginal

dryness or urogenital atrophy, and Spicer et al. teach the use of estrogenic compound such as estetrol for combating urogenital atrophy, and Willhite et al. teach that urogenital atrophy is vaginal dryness, one of ordinary skill would have been motivated to utilize the composition of Spicer et al. at a dose of at least 7.5 µg/day of an estrogenic compound as taught by Spicer et al. to treat vaginal dryness as disclosed by Sitruk-Ware et al. and use estetrol as the preferred compound in light of the disclosure of Spicer et al. with the reasonable expectation of providing a method that is efficacious in counteracting GnRH side effects including vaginal dryness.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1627

03/27/2010

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627